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Scrub typhus re-emergence in India: Contributing factors and way forward

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ABSTRACT

Scrub typhus is a mite borne infectious disease which has re-emerged in India in the 3rd millennium after years of quiescence. In this review, the authors hypothesize the various factors responsible for resurgence of this disease. The main drivers that could have contributed to the upsurge in scrub typhus cases in past two decades are changes in land use land cover (LULC) and urbanisation which are; as a result of the population explosion, causing a strain on sanitation and also increased diversion of forest land for agricultural use. In addition, the availability of better tests, changes in antimicrobial use, climate change also could have impacted the epidemiology, which is showing an upward trend as is evidenced by increasing reports and concomitant publications from India on scrub typhus. Scrub typhus cases are supposed to increase in the coming years as factors like global warming, urbanisation, changes in LULC and rise in AMR (anti-microbial resistance) will be difficult or impossible to control. Therefore, increasing awareness of public and health care professionals regarding scrub typhus coupled with availability of rapid diagnostic assays and implementation of appropriate treatment protocols for control of AFI (acute febrile illness) especially at the community level will help mitigate the scenario in the long run.

Introduction

Vector borne diseases have been known to mankind since antiquity [1]. Advances in diagnostics have made the detection of agents responsible for such diseases easier in the recent times [2]. A few diseases which were endemic in the past and were considered to be of less importance have again shown an upsurge in recent years. This phenomenon is known as re- emergence [3].

One such vector borne disease which has re-emerged in India in the 21st century is scrub typhus. The causative agent is *Orientia tsutsugamushi* and it is transmitted by the bite of chiggers (larvae) of mite, of the genus *Leptotrombidium* [4]. It can result in varied clinical presentations with the mortality in untreated cases reaching to even 40% [5].

This disease is mainly limited to the Asia Pacific region [6]. In India, there have been reports of this disease during and after the World War I, possibly because of overcrowding and other conducive conditions [7]. Scrub typhus in India was again described for the first time in the late 1990s from Vellore, after a period of quiescence. It was detected based on initial Weil- Felix test positivity followed by detection through specific tests [8]. Subsequently, it has re- emerged in various parts of India [9]; with reports from many states since the beginning of this millennium [10].

The reasons for this re-emergence of scrub typhus in the recent years are not known, as all data currently available is based on hospital and outbreak investigations of acute febrile illnesses. Therefore, based on a review of literature and their own considerable experience, the authors hypothesize that the following causes have led to a re-emergence of scrub typhus in India in recent times.

Probable factors responsible for scrub typhus resurgence in India: The hypotheses

(i) Changes in land use and urbanisation: The Indian population has been continuously expanding. There has been a rapid surge in population of India in the past few decades with an increase of about 181 million people between 2001 and 2011 [11]. The urban population in India has increased exponentially in recent years, from about 218 million in 1991, to 286 million in 2001 (27.81% of total population), and now 377 million in 2011 (31.16% of total population) [12]. There has been about 5% increase in urban population in the last two decades [13]. This population explosion and increased urbanisation has resulted in change in land use; such as, abandonment of agricultural lands and creation of transitional land cover, providing favourable environment for the chiggers of trombiculid mite. Thus, resulting in increased incidence or upsurge of scrub typhus cases [4,14]. Apart from these, urbanisation even

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increases stress on utilities, the sanitation suffers; resulting in garbage accumulation and increased rodent population, which are reservoirs of the infection [15]. This also contributes to a rise in rat-associated zoonoses, such as rickettsiosis [16]. A study by Park et al. [17], shows a similar rising trend in cases of scrub typhus in urban areas of South Korea, where its incidence was found to be much greater near the riverside, mountainous regions and in areas which are in close proximity with parks. This can be attributed to the eco-friendly trend of preserving the natural environment surrounding the city and having more number of parks in the city, which in turn creates a favourable environment for the reservoirs and vectors of the disease [18]. Also, with increasing urbanisation; the density of population has increased, resulting in increased availability of host which in this case are humans [11].

In addition, there has been a drastic change in the spatial patterns of forests and croplands of India since the late 1880s to early 2000s, mainly because of deforestation. In the early 1980s, majority of Indian lands were woody savanna but with increased focus on agriculture and urbanisation these lands were deforested, making way for croplands [19]. Conversion of dense forest to open/scrub forest and encroachment into forest areas has also played a role in the resurgence of scrub typhus.

Technically, forest cover has increased in certain areas; whereas dense and very dense forest cover has decreased [20]. This means more scrub forest, open forest, plantations and agricultural lands. In these areas, dense undergrowth can provide a refuge for the vector [21]. These vectors then go on and spread the disease, resulting in increased incidence of scrub typhus as observed in newer localities of India in the past few years [22].

Population explosion and resulting urbanisation has resulted in changes in forest cover (with a rise in number of open forests and scrub forests), increased population density and poor sanitation facilities. This has engendered a rise in rat population, which serves as a reservoir for the vector and disseminates scrub typhus. The aforementioned factors are difficult to control, especially as they require collaborative efforts between various stake holders (public and private). Therefore, scrub typhus is supposed to increase in the coming years.

(ii) Availability of specific tests: In the past decade, there has been an increase in the number of laboratories testing for scrub typhus in India. At Vellore, the IgM ELISA for scrub typhus was offered for routine testing (in addition to the existing Weil Felix test) since October 2002 [8,23]. Subsequently, many laboratories started testing for scrub typhus; as is evidenced by the published articles [10,24]. As a result more cases are now reported to the concerned authorities, while in the past many cases usually went unnoticed and undiagnosed because of mild symptoms and lack of specific diagnostic tests [25].

Design of new enzyme immunoassays in the 1990s and their widespread use in the past two decades has also led to improved diagnosis of scrub typhus [26–28] in India, as is evidenced by early publications from our centre [5,29,30] and other centres [10].

As a result of availability of better diagnostics, in all probability more number of scrub typhus cases will continue to be reported across India.

(iii) Host availability: In contemporary times, there has been an increase in the number of people who prefer keeping pets in India [31]. Increased numbers of pets can serve as hosts and reservoirs for the vectors [32], which could lead to increased transmission and rise in scrub typhus in the future.

(iv) Changes in antimicrobial prescription practices: Scrub typhus had virtually disappeared from India till the fading years of the 20th century [7,29,30]. The extensive use of tetracyclines for empiric treatment of acute undifferentiated fevers [33–35], whose broad spectrum of action includes *Orientia tsutsugamushi* [36,37] was responsible for this. Moreover, chloramphenicol, which is very effective against rickettsia [8,38] was also extensively used to treat enteric fever and other infectious diseases [39] till 1989 in India [40].

The scenario changed in the late 1990s with introduction of the more effective fluoroquinolones [41–44] and second and third generation cephalosporins [45–47] and the appearance of resistance [41,48–52], leading to reduced usage of chloramphenicol [39] and doxycycline [37] for febrile illnesses [53–55]. This was further compounded by the apprehensions regarding side effects of tetracyclines [56,57] and chloramphenicol [38]. This led to the extensive use of fluoroquinolones and cephalosporins for treatment of not only enteric fever [45–47] but also for empiric treatment of acute undifferentiated fevers in the last decade of the previous century [44,46]. Additionally, cephalosporins began to be extensively used for sepsis [58–60], UTI [61] and respiratory infections [62,63] during this time. This trend has continued till date [64–68], though these drugs are ineffective against rickettsial pathogens [69].

Macrolides, though effective against rickettsia including *O. tsutsugamushi,* are mainly prescribed for treatment of respiratory infections [70]. Additionally, majority of times scrub typhus is misdiagnosed as viral fever and thus not treated [71]. All these factors could have contributed to resurgence of this disease in the last two decades in India.

With the emergence of antimicrobial resistance, there has been a decline in the usage of tetracyclines and chloramphenicol for treatment of acute febrile illness [68]. This has led to an increased prescription of newer and more expensive broad spectrum antibiotics for these conditions [66,67]. As already alluded above, this will contribute not only to increased scrub typhus prevalence but also to associated morbidity and mortality. Creation of awareness amongst the public and medical fraternity with implementation of a robust antimicrobial stewardship program for treatment of febrile illnesses will be the best solution for reducing the disease burden.

(v) Meteorological factors: Observations from Vellore showed that the incidence of scrub typhus increased during the cooler months in Southern parts of India [29] and these cooler months (namely months from July to December) also correspond to months in which these areas receive rainfall [72]. Subsequent observations by Varghese et al. [73] and Gurung et al. [74] confirm that scrub typhus incidence is seasonal.

It is already known that chiggers thrive in humid conditions, with the optimal humidity for survival of chigger population being around 80% [75] and areas with high humidity are more prone to scrub typhus [76]. Temperature also plays a role, as demonstrated by Li et al. from China, that every 1 °C rise of temperature results in about 15% increase in scrub typhus cases [77]. In the past century, there has been a consistent rise in the average temperature of the Indian subcontinent [78]; which could have resulted in increased cases of scrub typhus.

With the current state of global warming, which according to authorities is an irreversible change and is supposed to continue over the years; the incidence of scrub typhus is speculated to rise continually [79,80].

(vi) Changes in human behaviour: In the present-day, humans have started indulging in a lot of leisure activities such trekking, camping etc., this results in increased exposure to the vector in its natural habitat and thus causes infections [81,82]. Raoult et al. [83], as early as in 1997, attributed the increase in scrub typhus cases to increased outdoor and leisure activities. These activities are projected to increase in the coming years and henceforth, the

scrub typhus cases are projected to rise in tandem with it [84].

Discussion

Scrub typhus is a vector borne disease with strong seasonal variation [29] and has re-emerged in India in this millennium [9,10]. This re-emergence can be attributed to multiple factors. The major role has been played by changes in land use and land cover (LULC), urbanisation [14,16,17], increased accessibility to specific tests for diagnosis of scrub typhus [8,23] and changes in antimicrobial prescription practices [53–55] in the past two decades.

These factors are either difficult to control or irreversible. Global warming, LULC changes and urbanisation are supposed to increase in future and this will in turn result in more number of scrub typhus cases. With increase in urbanisation and increased earning potential of the middle class, the outdoor leisure activities are also projected to rise [83,84]; bringing with itself the rise in scrub typhus cases every year. Further the indiscriminate use of broad spectrum antibiotics for febrile illnesses will add to the disease burden, especially associated complications and mortality. Added to this, availability of better tests (which need a standard laboratory set up), will likely increase the number of cases diagnosed.

Studies to determine disease burden, including seroprevalence and determination of risk factors will be useful to formulate and implement guidelines for prevention and treatment of this acute febrile illness. These guidelines should include drugs such as doxycycline in the empirical therapy, of recalcitrant fevers [7,8]; which will have an action on the underdiagnosed or misdiagnosed cases of scrub typhus [34,35], especially in primary and secondary care settings. As is known, the definitive diagnosis of scrub typhus (in the absence of eschar) is dependent mainly on serological assays [8]. Therefore, availability of good quality, economical, point of care tests (POCTs) will be helpful in timely detection of the disease resulting in prompt treatment, especially in resource poor conditions.

Scrub typhus being a vector borne zoonoses [4], public awareness campaigns are needed, emphasising on good sanitation (both general and personal), use of protective clothing and insect repellents to help reduce disease transmission. Healthcare workers, including medical doctors, also need to be educated so that scrub typhus is considered as a differential for all individuals presenting with acute febrile illness, even when the characteristic eschar is absent. All the above measures not only have the potential to reduce disease burden but have also been found to prevent morbidity and mortality in our centre in the current decade [85]. Prospective long term studies are needed to further understand the disease dynamics, so that focussed interventions can be designed and implemented for scrub typhus surveillance and control in India.

Conclusion

Scrub typhus cases are projected to increase in the coming years. Global warming, urbanisation and LULC changes, which impact scrub typhus incidence are difficult to control.

Therefore, to contain scrub typhus we propose increased awareness amongst public and healthcare personnel, availability of good quality point of care testing systems coupled with implementation of treatment protocols for acute febrile illness at community level.

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Conflict of interest statement

None.

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